REMARKS

Claims 1, 5-6, and 41 have been amended herein. Claims 26-33, 38-40, 46-53, and 59-61 have been canceled. Claims 62 and 63 are newly added. Claims 1-25, 34-37, 41-45, 54-58, 62, and 63 remain in the case.

Favorable reconsideration is respectfully requested.

The following remarks address the issues presented in the Office Action in the order of their appearance:

Supplemental Restriction Requirement:

Applicants acknowledge, with thanks, the Examiner's clarification of the prior Supplemental Restriction requirement. For the record, Applicants note that their interpretation of the prior requirement was based on the explicit language of Paper No. 9, dated 05/22/2002. Paper No. 9 clearly indicated that the restriction was "for examination purposes." (Office Action dated 05/22/2002, page 5, lines 10-11.) Paper No. 9 also indicated that Group I, elected pursuant to the initial restriction requirement dated 09/21/2001 was "generic," thus leaving the impression that the individual DNA sequences were species falling within the generic claims.

Applicants now being fully apprized of the Office's position, Applicants reiterate their traversal of the Supplemental Restriction Requirement as being contrary to both the letter and the spirit of MPEP §2434:

> **In most cases, up to 10 independent and distinct nucleotide sequences will be examined in a single application without restriction. . . . In some exceptional cases, the complex nature of the claimed material may necessitate that the reasonable number of sequences to be selected be less than 10.**

Applicants traverse the Supplemental Restriction Requirement because the Office has not shown why the present case is considered "exceptional" under MPEP §2434.

Moreover, as noted in their earlier response, <u>all</u> of the DNA molecules recited within the present claims encode human tryptases. Thus, <u>all</u> of these DNA molecules are very, very closely related. Specifically, as also noted earlier, <u>all</u> of the specifically recited

DNA molecules encode proteins that are identical, with the exception of codons that encode point mutations at amino acid positions 44, 91, and 194 (as numbered in Fig. 1 of the present application). Thus, for example, the elected SEQ. ID. NO: 20 contains 747 nucleotide bases within the coding sequence. Thus, if SEQ. ID. NO: 20 contained entirely different codons at the respective nucleotide positions encoding amino acid residues 44, 91, and 194, it would differ, at most, **by only nine nucleotides** from all of the other positively recited nucleotide sequences presented in the Sequence List. Nine nucleotides within a coding region of 747 nucleotides equals 1.20%. In other words, all of the sequences positively recited in the claims are 98.80% homologous.

Applicants therefore respectfully submit that while an election of species may be appropriate in the present circumstance, the Supplemental Restriction Requirement is not. The Office has not presented any sound scientific or technical reasons why the claimed nucleic acid sequences cannot be searched in their entirety.

Applicants further note that MPEP §803 indicates that even if an application contains claims drawn to independent or distinct inventions, the Office should search and examination of all the claims if examination on the merits can be done without serious burden. Because the nucleic acid sequences recited in the application are >98% homologous to one another, Applicants respectfully submit that all of the claims subject to the Supplemental Restriction Requirement can be examined without serious burden if the Supplemental Restriction Requirement **is not** required.

Objections to the Specification:

The objection to the specification is believed to have been addressed by appropriate amendments to Fig. 1 and to relevant portions of the specification. Applicants are also submitting herewith a Substitute Sequence Listing. Entry of the Substitute Sequence Listing is respectfully requested.

Drawings:

Formal drawings are attached hereto. Entry of the same is respectfully requested.

Objection to Claims 7-8 and 17-18:

This objection is noted. Applicants have traversed the Supplemental Restriction Requirement herein and therefore Claims 7-8 and 17-18 remain as originally submitted, pending final adjudication of the propriety of the Supplemental Restriction Requirement.

Rejection of Claims 1-12, 41, and 42 Under 35 USC §112, Second Paragraph:

This rejection is believed to have been overcome by appropriate amendment to the claims, in accordance with the Examiner's recommendation. Specifically, Claims 1 and 41 have been amended to recite that the host to be transformed is a "eukaryotic host cell."

Applicants submit that this rejection has now been overcome. Withdrawal of the same is respectfully requested.

Rejection of Claims 1-6, 9-16, 19-25, 34-37, and 41-42 Under 35 USC §112, First Paragraph:

As applied to Claims 1-6, 9-12, and 34-36, Applicants submit that this rejection has been overcome by amendment to the claims. Specifically, Claim 1 has been amended to recite the position within the encoded amino acid wherein the mutation is to appear. Because the specification clearly discloses how to bring about such mutations (see the entire Detailed Description and the Examples), this rejection is believed to have been overcome.

As applied to Claims 13-16, 19-25, 37, and 41-42, this rejection is respectfully traversed.

The rational for this rejection boils down to the simple proposition that the Office is of the opinion that Applicants have not enabled the invention because Applicants did not provide a sufficient number of working examples. Specifically, the Office Action states, in relevant part:

> The specification discloses one human β-I and one human β-II tryptase. The specification also discloses that the active sites of the tryptases disclosed in the specification... correspond to positions 44, 91, and 194 of the mature tryptase.... Furthermore the specification teaches the construction of several mutated forms of the human β-II tryptase in Table 1....
>
> * * *
>
> The specification only discloses **a few species** which is insufficient to put one of ordinary skill in the art in possession of (1) **all** attributes and features of **all** species within the genus; and (2) **all** attributes and features of **all** species falling within the genus of DNA constructs to practice the claimed method.

(Office Action dated February 21, 2003, p. 3)

This rejection is traversed because the above-quoted statement **is not** the yardstick by which enablement under §112, first paragraph is measured. Applicants are in no way required to define "**all**" attributes of "**all**" species falling within an genus in order to satisfy the dictates of §112, first paragraph. Applicants aren't even required to disclose a single species to satisfy the definition of an entire genus.

Section 112, first paragraph requires nothing more than that the specification enables a person of ordinary skill in the art how to make and use the claimed invention. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). **How** that teaching is provided **is not** dictated by the statutes, the regulations, the case law, or the MPEP.

In fact, the MPEP specifically dictates that defining a generic term either by (1) listing a number of exemplary species that fall within the generic term; and/or (2) using broader terminology, are both perfectly valid and **approved** approaches to defining a generic term. See MPEP §2164.08. See also *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971): "How a teaching is set forth, **by specific example** or **broad terminology**, is not important." (Emphasis added.)

Further still, it is improper to reject a claim under §112, first paragraph for not reciting various details or factors which must be presumed to be within the level of ordinary skill in the art. Again, see MPEP §2164.08; see also *In re Skrivan*, 166 USPQ 85, 88 (CCPA 1970). Lastly, Applicants are not required to disclose even a single

working example in order to enable an invention. See *In re Robbins*, 166 USPQ 552 (CCPA 1970).

Specifically addressing the merits of the present specification and the scope of the claims, note that **all** of the claims subject to this rejection are drawn to DNA sequences encoding "proteolytic tryptases." Tryptases themselves are an art-recognized class of enzymes, EC 3.4.21.59. See Exhibit A, attached hereto. Thus, they share the same core activity and catalyze the same core chemical transformation. As such, one of skill in the art is clearly aware (or can easily determine) the salient "attributes" of any given tryptase.

Applicants are not claiming **all** DNA constructs, which appears to be the point made in item (2) of the above-quoted passage from the Office Action. The claims are limited to DNA constructs that encode a defined polypeptide. Claim 13 is representative: Claim 13 requires a specifically named promoter, operationally linked to a secretion signal sequence, operationally linked to a DNA sequence "encoding proteolytic typtase having an active site mutation." Promoters and signal sequences are well known - Applicants recite a host of know promoter within Claim 13 itself. Linking these regulatory elements to a downstream coding sequence is also well known in the art. That which is well known in the art is best omitted from the specification and the claims. See *In re Buchner*, 18 USPQ2d 1331 (Fed. Cir. 1991).

However, linking them to a tryptase having an active site mutation is novel. And, a fact that is particularly relevant to the present rejection, the specification clearly notes the positions of the active site residues in tryptases. See Fig. 1 and the accompanying description beginning at page 30, line 14.

The specification clearly discloses, by way of both working examples **and** broad terminology, (1) how to obtain a gene for a desired tryptase (page 3, lines 13-18), (2) how and where to mutate the gene (page 30, line 14, to page 29, and Example 1c, beginning at page 34, line 1; (3) how to insert the gene into a suitable gene construct in operation relationship to promoters and secretion signals (page 17, line 25, to page 20, line 27); (4) how to insert the construct into a eukaryotic host (page 21, line 1, to page 23, line 18); and (5) how to isolate the expressed tryptase.

The specification provides working examples of how to generate an appropriate expression vector, see Examples 1a and 1b at page 33.

The specification provides working example of how to mutate the tryptase gene to induce the desired changes in the encoded protein, see Example 1c at page 34.

The specification provides a working example of transforming Pichia cells with several the several different constructs described in Example 1c. See Examples 2a, 2b, and 2c, starting at page 37 of the specification.

The specification provides a working example of how to purify the recombinant tryptases. See Example 5 at page 40 of the specification.

The specification provides extensive characterization of the enzymes so produced. See the Examples spanning pages 42-47.

In short, the specification provides a plethora of data, by way of a broad and wide-ranging discussion of how to accomplish each and every step required to practice the invention as broadly as it is claimed.

For the above reasons, Applicants submit that this rejection under §112, first paragraph, is improper. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1-6, 9-16, 19-25, 34-37, and 41-42 Under 35 USC §112, First Paragraph:

As applied to Claims 1-6, 9-12, and 34-36, Applicants submit that this rejection has been overcome by amendment to the claims. Specifically, Claim 1 has been amended to recite the position within the encoded amino acid wherein the mutation is to appear. Because the specification clearly discloses how to bring about such mutations (see the entire Detailed Description and the Examples), this rejection is believed to have been overcome.

As applied to Claims 13-16, 19-25, 37, and 41-42, this rejection is respectfully traversed. Applicants repeat the comments made in the prior section and incorporate the same herein.

The Office predicates this rejection on the unwarranted conclusion that the specification does not enable the fabrication of a construct containing a mutated proteolytic tryptase. The Office, however, fails to articulate why or in what manner the specification falls short. As noted earlier, the specification clearly dislcoses each and every step required to fabricate a mutated tryptase, regardless of its source. A tryptase is a tryptase, regardless of its origin. As noted earlier, and as evidenced by Exhibit A, tryptases are an art-recognized class of enzymes.

Again, the Office is clearly taking the position that Applicants must provide a certain base line number of working examples to enable the claims. This simply is not required by §112, first paragraph.

Regarding undue experimentation and the "Wands" considerations, note that the critical word in the phrase "undue experimentation" is "undue," not experimentation. The Office has the burden of providing sound scientific reasons, supported by the record, why the specification fails to properly enable the claims. (See, for instance, *In re Angstadt*, 190 USPQ 214 (CCPA 1976).) As part of that burden, the Office must present evidence showing that the disclosure requires **undue** experimentation. (*Id.* at 219.) In short, satisfaction of the enablement requirement of §112 is not voided by the necessity for some experimentation, such as routine screening. (*Id.*) A considerable amount of experimentation is permissible if it is routine or if the specification provides a reasonable amount of guidance with respect to how the experiments should proceed. See also *In re Jackson*, 217 USPQ 804 (Bd. App. 1982).

As noted earlier, the present specification provides a wealth of guidance on how to make the claimed constructs (commercial vectors are available, see page 17, line 25, to page 20, line 27), how to transform them into a suitable host cell, how to isolate the enzyme so produced, and how to characterize the enzyme so isolated.

Making the mutants is clearly described - it can be done using a commercially available kit; see page 30, lines 27-28. How to determine the activity (or inactivity) of the enzyme is accomplished by following the assays presented in the Examples. See pages 42-47.

In short, each and every step required to fabricate a mutated proteolytic tryptase is described in great detail in the specification. One of skill in the art is thereby enabled to chose a desired tryptase, chose the nucleotides to be altered, cause the mutations to happen, insert the mutated gene into a vector, transform the vector into a suitable host, and isolate the enzyme.

Sure, there might be a little experimentation along the way. But that is perfectly acceptable because the experimentation is not undue. Any experimention is part and parcel of the sometimes unpredictable nature of molecular biology. However, the specification clearly provides sufficient guidance on how to accomplish each step of the invention as claimed. Thus, this rejection is improper.

Applicants therefore submit that this rejection is untenable. Withdrawal of the same is respectfully requested.

Rejection of Claims 41 and 42 for Non-Statutory, Obviousness-type Double Patenting in View of U.S. Patent No. 6,274,366:

This rejection is rendered moot by the Terminal Disclaimer and required fee submitted herewith. Entry of the Terminal Disclaimer is respectfully requested.

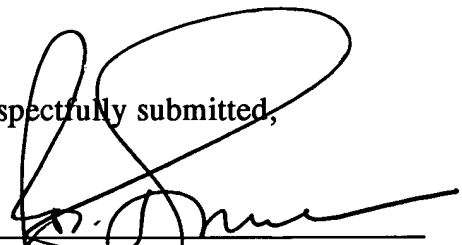
Withdrawal of this rejection is respectfully requested.

CONCLUSION

In light of the above amendment, accompanying remarks, formal figures, and Supplemental Sequence List submitted herewith, Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

The Commissioner is hereby authorized to charge any additional fees or credit any overpayment to Deposit Account No. 18-2055.

Respectfully submitted,



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